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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,510	02/08/2002	Edwin Clark	MRI-027	3451

959 7590 06/01/2006

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	10/071,510	CLARK ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,70 and 71* is/are pending in the application.

4a) Of the above claim(s) *2,3,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,11-14,70 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____. .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed April 6, 2006, is acknowledged and has been entered. Claims 14-69 have been canceled. Claims 1-14 have been amended. Claims 70 and 71 have been added.

2. Receipt of the substitute declaration filed April 6, 2006, is acknowledged.

3. Receipt of the substitute specification and the corresponding marked-up copy filed April 6, 2006, is acknowledged.

Applicant is reminded that a copy of the prior set of claims should not be provided as part of a substitute specification.

4. Claims 1-14, 70, and 71 re pending in the application. Claims 2, 3, 9, and 10 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species of invention, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on June 29, 2004 and June 23, 2005.

5. Claims 1, 4-8, 11-14, 70, and 71 are currently under prosecution.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Oath/Declaration

8. The substitute oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The substitute oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Election/Restrictions

9. Newly amended claims 1, 5-8, 11-14, 70, and 71 are directed to an invention(s) that is (are) independent or distinct from the invention originally claimed for the following reasons:

The originally presented claims, insofar as those claims were directed to the elected invention, were drawn to a process for determining whether an agent can be used to reduce the growth of a tumor, said process comprising obtaining a sample of tumor cells and determining whether the tumor cells express one or more sensitivity markers, wherein said "agent" is a combination of a taxane compound and a platinum compound.

The present claims are directed to any "agent" selected from the group consisting of TAXOL, TAXOL mimics, TAXOL analogs, TAXOL derivatives, cisplatin, cisplatin mimics, cisplatin analogs and cisplatin derivatives, as opposed to an agent selected from the group consisting of (a) a taxane compound, (b) a plantinum compound, and (c) a combination of agents consisting of a taxane compound and a platinum compound.

Since, for example, a "TAXOL mimic" or a "TAXOL derivative" is not necessarily a "taxane compound" and a "cisplatin mimic" or "cisplatin derivative" is not necessarily a "platinum compound", the present claims encompass subject matter that differs from the subject matter to which the originally presented claims were drawn.

This interpretation is supported by any of a multitude of disclosures, such as the disclosure at paragraph [0267] of the published application[1], which states the following:

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[1] U.S. Patent Application Publication No. 2003/0143552 A1.

> Cisplatin is a chemical compound within a family of platinum coordination complexes which are art-recognized as being a family of related compounds. Cisplatin was the first platinum compound shown to have anti-malignant properties. The language "platinum compounds" is intended to include cisplatin, compounds which are structurally similar to cisplatin, as well as analogs and derivatives of cisplatin. The language "platinum compounds" can also include "mimics". "Mimics" is intended to include compounds which may not be structurally similar to cisplatin but mimic the therapeutic activity of cisplatin or structurally related compounds in vivo.

Accordingly, the term "cisplatin mimic", for example, is broadly but reasonably interpreted to encompass any compound that mimics the therapeutic activity of cisplatin or a structurally related compound, but which itself is not necessarily structurally similar thereto. Thus, the "cisplatin mimic", for example, to which the claims are directed need not be a "platinum compound"; and, given the similar disclosure at paragraph [0252] of the published application, a "TAXOL mimic", for example, need to be "a taxane compound".

In addition, as amended, claim 4 is presently drawn to a process for determining whether an agent can be used to reduce the growth of an ovarian tumor, said process comprising obtaining a sample of ovarian tumor cells and determining whether the tumor cells express one or more sensitivity markers, wherein said "agent" is a combination of "two or more agents consisting of TAXOL, TAXOL mimics, TAXOL analogs, TAXOL derivatives, cisplatin, cisplatin mimics, cisplatin analogs and cisplatin derivatives", as opposed to an agent selected from the group consisting of (a) a taxane compound, (b) a plantinum compound, and (c) a combination of agents consisting of a taxane compound and a platinum compound. Thus, whereas the originally presented claims were examined to the extent those claims were directed to a combination of agents consisting of a taxane compound and a platinum compound, claim 4 is now directed to a combination of *two or more agents* selected from the specified group, and not necessarily to a combination of one taxane and one platinum compound.

Because of the above noted difference in breadth of the present claims and the originally presented claims, the search necessary to examine the full breadth of the present claims is not the same, nor is it necessarily coextensive with the search already performed; therefore, a consideration of the merit of the present claims to any extent

beyond the breadth of the originally presented claims would require the performance of a new and different search, which would constitute a serious burden.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1, 5-8, 11-14, 70, and 71 have only been considered to the extent the claims are deemed to read on the elected, originally presented invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Grounds of Objection and Rejection Withdrawn

10. Unless specifically reiterated below, Applicant's amendment and/or arguments filed April 6, 2006, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed October 6, 2005.

Grounds of Objection and Rejection Maintained

Specification

11. The objection to the specification because of disclosures by the impermissible referral to embedded hyperlinks and/or other forms of browser-executable code, and to the Internet contents so identified, is maintained. Reference to hyperlinks and/or other forms of browser-executable code, and thus to the Internet contents so identified, *is impermissible and therefore requires deletion*.

In replying to the preceding amendment, Applicant amended the specification to delete "http://" from the disclosure at page 25, line 37; however, the specification still contains a link, namely "www.ncbi.nlm.nih.gov". Even if it were the link were "inactivated", the disclosure still refers to the website, and to the Internet contents so identified.

Notably, additional examples of such impermissible references appear in the substitute specification at page 71, lines 29 and 33.

Again, the attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-

executable code, for example, (i.e., any reference to the contents of an Internet website) is considered to be an improper incorporation by reference and requires deletion.

By way of further explanation, MPEP 608.01(p) does not provide for incorporation of essential *or* non-essential material by reference to, for example, hyperlinks or other forms of browser-executable code. Essential subject matter may only be incorporated by reference to (1) US patents and pending US applications, or patents or other publications published by a foreign country or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates material by reference, or (4) a foreign application. Non-essential information may be incorporated by reference to (1) patents or applications published by the United States, or patents or other publications published by a foreign country or a regional patent office, (2) prior filed, commonly owned US applications, (3) non-patent publications.

It is impermissible that a patent's disclosure incorporate essential or non-essential material by reference to, for example, embedded hyperlinks and/or other forms of browser-executable code, because the information contained in the websites or databases to which the hyperlinks or other forms of browser-executable code connect may not be maintained on the Internet for the duration of the patent's term and may not contain the same information after the filing date of an application that was contained in the website or database on or before the filing date of the application. Since the information contained in a website may vary, it is not evident that information contained in a website will always remain useful the practitioner or even applicable to the invention; and information contained in an extinct website cannot possibly be helpful to the practitioner. Furthermore, the validity of a patent containing a reference to a hyperlink or other form of browser-executable code may be reasonably questioned if the website(s) to which the hyperlink(s) connect were relied upon by the patentee(s) to provide sufficient disclosure or description of the invention to meet the requirements of 35 USC § 112, first and second paragraphs. As such, recitation of such references is not permitted.

A hyperlink or other form of browser-executable code may be permitted if the hyperlink or other form of browser-executable code is part of the claimed invention, but

in such a case, the Office would disable the hyperlink or other form of browser-executable code.

In general, if the Applicant expects to rely upon the information contained in the websites or databases referred to by such disclosures to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph, or to provide antecedent basis for the subject matter of claims in the instant application or related applications, and if the material is properly incorporated by reference in the referencing application, Applicant would be required to amend the specification of the referencing application to include the material incorporated by reference to the hyperlink or other forms of browser-executable web, or other non-permissible sources and to provide a declaration by Applicant or Applicant's representative stating that the amendatory material consists of the same material incorporated by reference in this application. See MPEP § 608.01(p).

If Applicant intends that information contained at the websites to which the disclosures refer be incorporated, Applicant is required to amend the specification to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

12. The objection to the specification, because the use of improperly demarcated trademarks, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant has made a bona fide attempt to resolve this issue by the submission of a substitute specification, an additional example of such an improperly demarcated trademark is found in the specification at page 65, line 12 (i.e., Qiagen™).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

13. The objection to claims 1, 4-8, 11-14, 70, and 71, as being drawn to the subject matter of non-elected species of invention, is maintained.

Claim Rejections - 35 USC § 112

14. The rejection of claims 1, 4-8, 11-14, 70, and 71 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At pages 8-11 of the amendment filed April 6, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As presently amended, claims 1, 4, 7, 8, and 14 are broadly drawn to a method for determining whether an agent can or cannot be used to reduce the growth of an ovarian tumor comprising determining the expression of one or more sensitivity markers, including the marker of SEQ ID NO: 16.

As explained in the preceding Office action, the term "marker" is defined in the specification to mean a nucleic acid molecule corresponding to a polynucleotide sequence, which in this instance is the species of marker identified as SEQ ID NO: 16. According to the definition provided, the term is meant to include, for example, a

messenger RNA (mRNA) and a gene (i.e., a genomic DNA molecule comprising introns and exons, which is transcribed to yield a messenger RNA (mRNA) molecule corresponding to the sequence set forth as SEQ ID NO: 16). Accordingly, claims 1, 4, 7, 8, and 14 are directed to a gene corresponding to the sequence set forth as SEQ ID NO: 16 or an RNA transcript thereof (i.e., a mRNA transcribed from the gene).

In contrast, claims 6 and 13 are directed to a method for determining whether an agent can or cannot be used to reduce the growth of an ovarian tumor comprising determining the expression of the marker of SEQ ID NO: 16 by detecting the amount of protein that is encoded by the marker.

Notably claims 5 and 12 have been amended so as to be directed to "SEQ ID NO:16 mRNA". However, as explained below in the new grounds of rejection under 35 U.S.C. § 112, second paragraph, this term (i.e., "SEQ ID NO:16 mRNA") does not appear to be defined, and moreover, the specified polynucleotide sequence is not an RNA sequence. As such, it is not evident to which particular mRNA molecule the claims are directed.

As further explained in the preceding Office action, the term "agent" is defined broadly as "anything that cancer cells, including tumor cells, may be exposed to in a therapeutic protocol" (page 10, lines 12-21, of the originally filed specification). Thus, it is evident that the term "agent" includes any compound or any combination of a multitude of compounds that may have be used to reduce the growth of a tumor.

Notably Applicant has amended the claims to recite a limitation requiring the "agent" to be selected from the group consisting of TAXOL, TAXOL mimics, TAXOL analogs, TAXOL derivatives, cisplatin, cisplatin mimics, cisplatin analogs and cisplatin derivatives. As explained below in the new grounds of rejection under 35 U.S.C. § 112, second paragraph, the identification/description of the TAXOL, TAXOL mimics, TAXOL analogs, and TAXOL derivatives to which the claims are directed is indefinite because TAXOL is a tradname/trademark. Furthermore, as explained above in the section headed "***Election/Restrictions***", the claims might reasonably be interpreted as actually broader in scope than the originally presented claims since, for example, neither a

"TAXOL mimic" nor a "cisplatin mimic" is necessarily a "taxane" or a "platinum compound", per se.

As also explained in the preceding Office action, the specification discloses, "cancer cells, including tumor cells, refer to cells that divide at an abnormal (increased) rate" (page 13, lines 10 and 11, of the originally filed specification).

Notably claims 1, 7, 8, and 14 have been amended to recite the term "ovarian". Accordingly, the scope of claims 1, 4-8, 11-14, 70, and 71 is now limited to a method comprising determining whether *ovarian* cells that divide at an abnormal (increased) rate express one or more markers, including the marker of SEQ ID NO: 16 or a protein encoded thereby.

Applicant has argued the written description requirement has been met, as the specification would reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. However, given the fact that the claims are directed to a variety of structurally and/or functionally distinct compounds, which are not necessarily "taxanes" or "platinum compounds" per se, and moreover not necessarily Taxol™ or cisplatin, it is submitted the specification would not permit the skilled artisan immediately envision, recognize or distinguish at least a substantial number of these compounds, so as to recognize that Applicant did in fact have possession of the claimed invention at the time the application was filed.

Applicant has argued the specification describes particularly identifying structural and functional features of the members of the genus of compounds to which the claims are directed. In response, because the compounds may vary so substantially in both structure and function, it is not apparent which particular features of those particularly described members should be regarded as sufficiently descriptive of the genus as a whole. Again, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes at least a substantial number of the members of the structurally and functionally disparate agents to which the claims are directed. A description of what a material does, or might do, rather than of what it is, does not suffice to describe the claimed invention. See

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001; hereafter "Guidelines").

Furthermore, it is again submitted that to adequately describe the claimed invention, it would be necessary to describe correlations between the expression of one or more adequately described markers in ovarian tumor cells and their sensitivity, or lack thereof, to at least a representative number of members of the genus of agents to which the claims are directed. While the specification describes a correlation between the presence of one or more adequately described markers in ovarian cancer cells and their sensitivity or lack thereof to a combination of Taxol™ (paclitaxel) and cisplatin, it would not suffice to adequately describe the claimed invention, such as to reasonably convey to the skilled artisan that Applicant had possession of that invention at the time the application was filed. This is because the combination of Taxol™ and cisplatin is not representative of the whole of the genus of agents to which the claims are directed. Because of the markedly different structures, specificities, modes of action, additive and/or synergistic effects of different types of agents to which the claims are directed, the presence of one or more markers in any given tumor may not always correlate with its sensitivity to the agents.

Applicant has argued that the amendment of the claims has resolved this issue, as the claims are now directed to a genus of agents selected from the group consisting of TAXOL, TAXOL mimics, TAXOL analogs, TAXOL derivatives, cisplatin, cisplatin mimics, cisplatin analogs and cisplatin derivatives. This argument is not persuasive for the reasons already addressed herein, as well as in the preceding Office action.

Furthermore, it is again aptly noted that the specification does not describe a genomic DNA molecule (i.e., a gene) corresponding to the nucleotide sequence identified as SEQ ID NO: 16. A description of the nucleotide sequence of a complementary DNA (cDNA) molecule derived from a transcript (i.e., messenger RNA (mRNA) molecule), such as the nucleotide sequence of SEQ ID NO: 16 does not suffice to describe the structure of a corresponding gene, and particularly the structure of the introns of which the gene is comprised, as the mRNA molecule contains no information

that could be used to glean the structure of either the introns or the gene. Given the definition of the term "marker", as recited in the claims, absent a detailed description of the gene corresponding to the nucleotide sequence of SEQ ID NO: 16, the disclosure would not reasonably convey Applicant's possession of the claimed invention at the time the application was filed.

Applicant has argued that one need not have described the gene corresponding to the marker of SEQ ID NO: 16 to have described the claimed invention. Provided the marker were limited to a mRNA molecule comprising the complement of the polynucleotide sequence of SEQ ID NO: 16, it is agreed it would not be necessary to known the structure of the gene transcribed to produce that mRNA molecule. If, on the other hand, the marker is not necessarily the mRNA comprising the complement of SEQ ID NO: 16 but rather any other "marker" (e.g., a alternative transcript, resulting from alternative splicing), which might be said to correspond to "the marker of SEQ ID NO: 16", it is submitted that it would be necessary to know the structure of the gene, or otherwise the structures of other such "markers" to recognize that Applicant did indeed have possession of the claimed invention at the time the application was filed.

Finally, the specification discloses the nucleotide sequence of SEQ ID NO: 16 *is novel* and does not teach whether the nucleotide sequence encodes all or part of a protein. Yet, claims 6 and 13 are specifically directed to methods comprising determining whether tumor cells express one or more markers, including a marker corresponding to the nucleotide sequence of SEQ ID NO: 16 by detecting and quantifying the amount of protein that is encoded by those markers. Absent a description of the protein encoded by those markers, and particularly of the protein encoded by a marker corresponding to the nucleotide sequence of SEQ ID NO: 16, the disclosure would not reasonably convey Applicant's possession of the claimed invention at the time the application was filed.

Applicant has argued that the skilled artisan would conclude Applicant was in possession of the claimed invention because the Federal Circuit indicated once the nucleotide sequence of an isolated cDNA is known, the amino acid sequence of the protein encoded by the cDNA may be predicted. In response, the claims are directed to

a process for determining whether or not an agent can be used to reduce the growth ovarian tumor cells, said method comprising determining whether tumor cells express one or more markers, including a marker corresponding to the nucleotide sequence of SEQ ID NO: 16 by detecting and quantifying the amount of protein that is encoded by those markers. As explained, if the gene is novel and it is not known whether the nucleotide sequence encodes all or part of a protein, why should the disclosure be regarded as having sufficiently described the claimed invention so as to reasonably convey its possession by Applicant at the time the application was filed?

Again, Guidelines states rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

Here, the claims are directed to a process that *has not been described* inasmuch as it comprises detecting the level of a protein that has not been described. While one may indeed predict the amino acid sequence of the protein(s) that might be encoded by any given isolated cDNA molecule, one may not so easily predict whether the level of a protein encoded the marker of SEQ ID NO: 16 provides an indication of whether or not an agent can be used to reduce the growth of an ovarian tumor, since, for example, the processes of transcription and translation are not always coordinately regulated. Nowhere in the specification is the structure of the protein encoded by the marker of SEQ ID NO: 16 described; and moreover nowhere is its abundance correlated with either the level of the mRNA comprising the complement of SEQ ID NO: 16 or the susceptibility of ovarian cancer cells to any one combination of a taxane and a platinum compound. Thus, apart from the language of the claims, there is no disclosure that would reasonably convey possession of the claimed invention at the time the application was filed.

15. The rejection of claims 1, 4-8, 11-14, 70, and 71 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At pages 11-17 of the amendment filed April 6, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained above in the written description rejection, as well as in the preceding Office action, the claims are directed to a method for determining whether any member of a genus of structurally and functionally different agents can or cannot be used to reduce the growth of ovarian tumor cells, said method comprising obtaining a sample of ovarian tumor cells and determining whether the tumor cells express one or more markers, wherein at least one of said markers is a marker corresponding to the polynucleotide sequence of SEQ ID NO: 16.

Again, the specification merely describes the correlation of one or more markers, including a marker identified by the nucleotide sequence set forth as SEQ ID NO: 16 and the sensitivity of ovarian cancer cells to the combination of Taxol™ (paclitaxel) and cisplatin. No other correlation between the expression of these one or more markers and the sensitivity, or lack thereof, of any other type of cancer to any other agent has been described.

Applicant has argued that the claims are not directed to a method for treatment, a fact that is not disputed.

Applicant has argued the appropriate inquiry is a determination of whether or not the specification teaches the ordinary skilled artisan to assess the expression of a marker corresponding to SEQ ID NO: 16. To the contrary, however, as the invention is *not* a method for assessing the expression of the marker, but rather a method for determining whether or not a combination of a taxane and a platinum compound can be used to reduce the growth of an ovarian tumor, the appropriate inquiry is a determination of whether or not the specification would have taught the skilled artisan, as of the earliest effective filing date sought, to assess the susceptibility of an ovarian tumor to the growth inhibitory effects of any given combination of a taxane and a platinum compound by determining the expression of the marker of SEQ ID NO: 16 *without undue and/or unreasonable experimentation*.

As explained previously, before the skilled artisan could use the claimed invention, it would be necessary to determine whether correlations exist between the presence and/or levels of expression of one or more adequately described markers (including the marker of SEQ ID NO: 16) in ovarian tumors and their sensitivity, or lack

thereof, to at least a representative number of members of the genus of agents to which the claims are directed. Therefore, while the specification teaches a correlation between the presence of one or more adequately described markers in ovarian cancer cells and their sensitivity or lack thereof to a combination of Taxol™ (paclitaxel) and cisplatin, this amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the breadth of the claims and would not be sufficient to enable the skilled artisan to use the claimed invention without undue and unreasonable experimentation.

There are many reasons the disclosure would not be sufficient to enable the skilled artisan to use the claimed invention without undue and unreasonable experimentation. The combination of Taxol™ and cisplatin is not representative of the whole of the genus of agents to which the claims are directed because the claims are directed to any combination of a taxane and a platinum compound, wherein these compounds have markedly different structures, specificities, modes of action, additive and/or synergistic effects of different agents. Consequently, the presence of one or more markers in any given tumor may not always correlate with its sensitivity to the agents. As such, the existence of such correlations cannot be predicted or known beforehand, but only determined empirically.

As also explained in the preceding Office action, these conclusions are supported by the teachings of Abuharbeid et al. (of record), for example. Again, Abuharbeid et al. teaches that overexpression of HER-2 in breast cancer cell lines can confer resistance to paclitaxel; see entire document (e.g., page 142, column 1). However, for ovarian carcinoma cells, Abuharbeid et al. teaches there is conflicting data (page 142, column 1). Abuharbeid et al. discloses that reduction of HER-2 expression in a Her-2-overexpressing ovarian carcinoma cell line leads to increased resistance to paclitaxel, an observation which is at odds with the effect of its overexpression in breast cancer cell lines (page 142, column 2); yet, in another ovarian cancer cell line, a reduction in HER-2 expression led to increased sensitivity to the drug (page 142, paragraph bridging columns). These observations led Abuharbeid et al. to perform a study comparing the effects of inhibiting the expression of HER-2 by three independent

targeting strategies upon the sensitivity of an ovarian cancer cell line to paclitaxel; they found that each of the different means by which HER-2 expression was inhibited led to different effects upon the cells' sensitivity to the drug (e.g., the abstract). Thus, the teachings of Abuherbeid et al. underscore the unpredictable nature of the art of determining the sensitivity or insensitivity of cancer cells to an agent by determining and comparing the level of expression of a marker.

As further explained in the preceding Office action, it is nevertheless feasible that a gene expression profile may be determined which identifies particular types of cancer that are sensitive, or not, to particular agents or combinations of agents. For example, Ayers et al. (of record) concludes that transcriptional profiling has at least the potential to be used to identify a gene expression pattern in breast cancer that may lead to clinically useful predictors of pathologic complete response to certain neoadjuvant combinatorial therapy; see entire document (e.g., the abstract). Even so, Ayers et al. concludes that their study revealed no single marker sufficient associated with pathologic complete response to be used as an individual predictor (abstract).

Although the specification asserts that a correlation exists between one or more of the disclosed markers, including a marker identified by the nucleotide sequence set forth as SEQ ID NO: 16 and the sensitivity of ovarian cancer cells to the combination of Taxol™ (paclitaxel) and cisplatin, the use of the claimed invention to determine whether an agent can or cannot be used to reduce the growth of a tumor has not been exemplified. Although the specification discloses statistical algorithms were used to establish the correlation (page 65), the algorithms and methodology used in the analyses performed have not been described, such that it would be possible to repeat such analyses using other agents and other types of tumors.

Applicant has argued the Office has not met its burden of establishing a prima facie case that the specification would not be sufficiently enabling. The Examiner disagrees; for the reasons reiterated herein, as well as discussed previously, the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the breadth of the claims and would not reasonably enable the skilled artisan to practice the claimed invention without undue and/or unreasonable experimentation.

Applicant has argued that the teachings of Abuherbeid et al. are irrelevant; the Examiner disagrees, as the marker of SEQ ID NO: 16 is purported to be novel. It follows that there would be no reports published that might contradict the asserted utility of the claimed invention; and moreover the novelty of the marker alone does not serve to dispel the actual issue at hand, but only serves to strengthen the position taken that given the evident level of unpredictability in the art, the guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the practice of the claimed invention, absent undue and/or unreasonable experimentation.

Applicant has further remarked that Ayers et al. is irrelevant because the publication does not report an evaluation of the expression of the marker of SEQ ID NO: 16; however, this remark also fails to address the actual issue, which is, given such evident unpredictability, whether or not the disclosure should be fairly regarded as reasonably enabling the skilled artisan to use the claimed invention to assess the sensitivity of ovarian tumor cells to any combination of a taxane and a platinum compound by determining if the marker of SEQ ID NO: 16 is expressed in those cells. Again, Ayers et al. concludes that their study revealed no single marker is sufficiently associated with pathologic complete response to be used as an individual predictor that response. While Ayers et al. does not report the expression of the novel marker disclosed in this application, the reference argues the need for further validation of the practice of the claimed invention; and given the disparity in the breadth of the claims and the breadth of the disclosure, such further validation falls well within experimentation of such an amount and level of complexity as to be regarded undue and unreasonable.

Applicant has submitted that Guy et al. (attached to Applicant's response as Exhibit A) proves the skilled artisan could make derivatives of TAXOL. Guy et al. does in fact review the development of fluorescent taxoids, which are suited for use in fluorescent microscopic studies. Guy et al., however, does not remedy the insufficiency of the instant disclosure to reasonably enable the practice of the claimed invention; moreover, Guy et al. does not appear to discuss the relationship between the

expression of the marker of SEQ ID NO: 16 in ovarian tumors and their sensitivity to any given combination of a taxane and a platinum compound.

Applicant has argued the specification teaches methods for assessing the expression of the disclosed markers. In reply, Applicant is reminded the specification need not, and preferably omits such general teachings, especially as the methods described were both well known and conventional as of the earliest filing date sought. The description of the general methodologies by which the expression of a gene is assessed does not serve to remedy the issue at hand.

Applicant has argued the algorithms used to determine the relationship between the expression of the disclosed markers in ovarian tumors and their susceptibility to the growth inhibitory effects of the combination of Taxol™ (paclitaxel) and cisplatin need not have been taught to enable the skilled artisan to use the claimed invention because the markers having such an association have been described. In response, the claims are not solely limited to a method for assessing whether the combination of Taxol™ (paclitaxel) and cisplatin can be used to reduce the growth of an ovarian tumor, but are instead broadly drawn methods for assessing the susceptibility of ovarian tumors to combination of any of a large number of structurally and/or functionally disparate taxanes and any of a large number of structurally and/or functionally disparate platinum compounds.

In the next paragraph, it appears that Applicant has contrarily argued that the algorithms necessary to practice the claimed invention were known in the art at the time the application was filed; and Applicant has referred to a number of regression models, which were known in the art at time of filing, which are contended to be useful in practicing the claimed invention. In response, the specification pointedly fails to teach which of the known models should be used in practicing the claimed invention; if knowledge of the appropriate algorithm and methodology are in fact necessary to determine whether the invention can be practiced, it is submitted that the disclosure should have made clear which algorithm and methodology were used to establish the utility of its exemplified use in assessing whether ovarian tumors are susceptible to the combination of TAXOL and cisplatin.

Furthermore, as explained previously, in accordance with claim 1, the mere presence of one or more markers in the tumor cells identifies the cells as having sensitivity to the agent, such that the agent may be used to reduce the growth of the tumor cells. However, according to claim 8, is it not just the mere presence of one or more markers, but rather their complete absence or their relatively lower abundance that identifies the cells as not having sensitivity to the agent. Again, why is that the absence or underexpression of the one or more markers and the tumor cells' insensitivity to an agent are inversely correlated, whereas it is merely the presence of the marker, rather than its overexpression that allegedly positively correlates with the tumor cells' sensitivity to the agent? In practicing the invention of claim 1, if the markers are present, the tumor cell is identified as sensitive to the agent; it would follow logically that if the markers are not present, the tumor cell is identified as lacking sensitivity to the agent. Yet, in practicing the invention of claim 8, it paradoxically seems that the mere presence of the markers in the tumor cells fails to identify the cells as having sensitivity to the agent, as instead tumor cells that underexpress the markers are identified as lacking sensitivity.

Then, with particular regard to the marker corresponding to the nucleic acid sequence set forth as SEQ ID NO: 16, the specification teaches only that it is a marker of sensitivity, as opposed to a marker of resistance. The specification fails to teach whether it is the mere presence of such markers, or their relative levels of expression that correlate with tumor cells' sensitivities to agents. If it the level of expression of the markers, rather than their mere presence, that identifies a tumor cell has having sensitivity to an agent, it is duly noted that the specification provides insufficient guidance and direction to use the claimed invention without undue and unreasonable experimentation, since, for example, the disclosure does not provide a description of the standard to which such comparisons of the levels of expression are to be made. When is the marker underexpressed? How does one determine if it is underexpressed, when there is no standard for ascertaining whether it is underexpressed?

Finally, further regarding claims 1 and 8, while the specification discloses a correlation between the sensitivity of ovarian cancer cells to a combination of paclitaxel

and cisplatin and the presence, or level of expression of one or more markers in those cells, it does not show a correlation between the sensitivity of the cells to either paclitaxel or cisplatin alone, or any other drug or combination of drugs. It is submitted that because each different drug in a given combination has, for example, a discrete mode of operation, and because the drugs may have additive or synergistic, or counteractive effects upon the growth of particular tumor cells, it is submitted that it is not possible to extrapolate the data presented in this application to reliably predict the effects of the different drugs alone.

In conclusion, although Applicant's arguments have been carefully considered, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there is a preponderance of factual evidence, scientific reasoning, and logic arguing the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to have enabled the practice of the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

New Grounds of Rejection

16. Claims 1, 4-8, 11-14, 70, and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-8, 11-14, 70, and 71 contain the trademark/trade name TAXOL. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade

name is used to identify/describe paclitaxel, mimics thereof, analogs thereof, or derivatives thereof and, accordingly, the identification/description is indefinite.

Claims 5 and 12 are indefinite because the claims recite the term "SEQ ID NO: 16 mRNA". The polynucleotide sequence of SEQ ID NO: 16 is not the sequence of an RNA molecule; and the term "SEQ ID NO: 16 mRNA" is not defined in the specification. Therefore, it is not apparent to which mRNA molecule the claim refers. Consequently, the metes and bounds of the subject matter that Applicant regards as the invention cannot be determined with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Conclusion

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
May 31, 2006